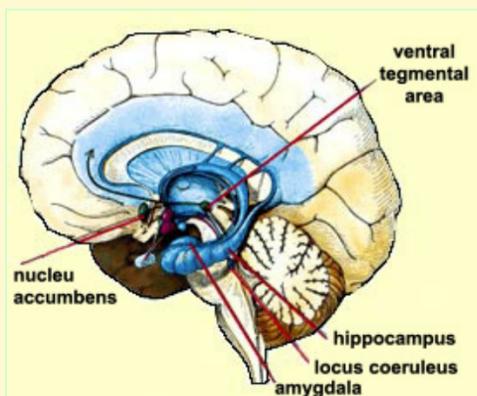




## KARG >> Addiction Related Brain Regions

Several brain regions have been implicated in addiction, including nucleus accumbens, ventral tegmental area, prefrontal cortex, locus coeruleus and another two structures in the limbic system: amygdala and hippocampus. Some information comes from Wikipedia.



## Overview of Addiction Related Brain Regions

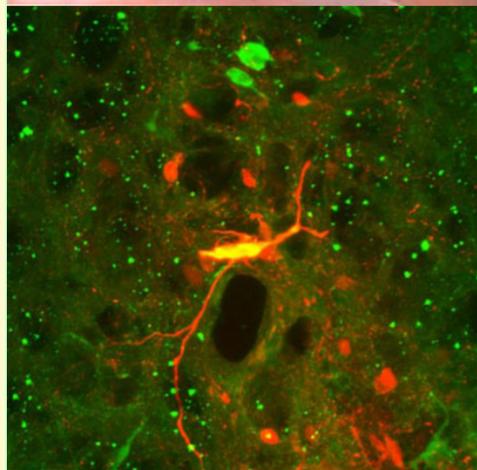
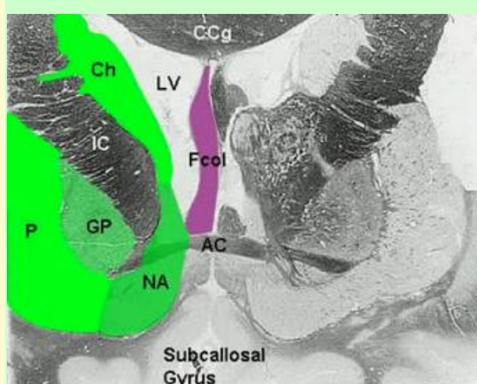
The **nucleus accumbens** definitely plays a central role in the reward circuit. Its operation is based chiefly on two essential neurotransmitters: dopamine, which promotes desire, and serotonin, whose effects include satiety and inhibition. Many animal studies have shown that all drugs increase the production of dopamine in the nucleus accumbens, while reducing that of serotonin.

But the nucleus accumbens does not work in isolation. It maintains close relations with other centres involved in the mechanisms of pleasure, and in particular, with the **ventral tegmental area (VTA)**. Located in the midbrain, at the top of the brainstem, the VTA is one of the most primitive parts of the brain. It is the neurons of the VTA that synthesize dopamine, which their axons then send to the nucleus accumbens. The VTA is also influenced by endorphins whose receptors are targeted by opiate drugs such as heroin and morphine.

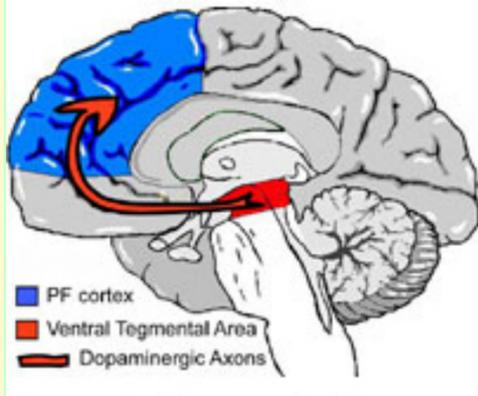
Another structure involved in pleasure mechanisms is the **prefrontal cortex**, whose role in planning and motivating action is well established. The prefrontal cortex is a significant relay in the reward circuit and also is modulated by dopamine.

The **locus coeruleus**, an alarm centre of the brain and packed with norepinephrine, is another brain structure that plays an important role in drug addiction. When stimulated by a lack of the drug in question, the locus coeruleus drives the addict to do anything necessary to obtain a fix.

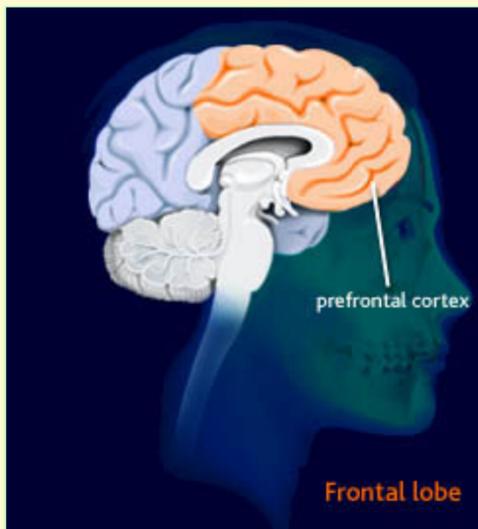
Two structures in the limbic system also play an active part in the pleasure circuit and, consequently, in drug dependency. The first is the **amygdala**, which imparts agreeable or disagreeable affective colorations to perceptions. The second is the **hippocampus**, the foundation of memory, which preserves the agreeable memories associated with taking the drug and, by association, all of the details of the environment in which it is taken. Sometime in the future, these details may reawaken the desire to take the drug and perhaps contribute to recidivism in the patient.



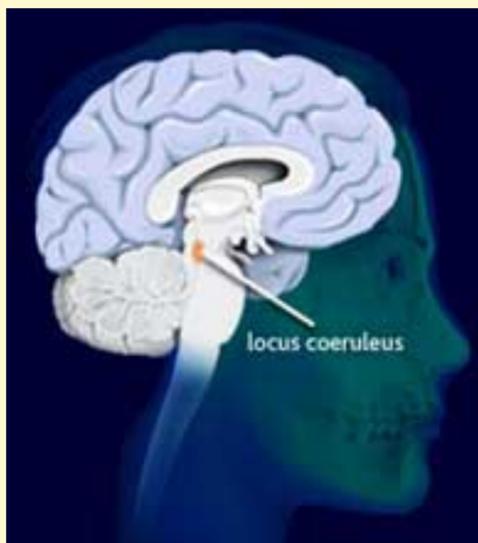
**Nucleus Accumbens (NAc)** is a collection of neurons located where the head of the caudate and the anterior portion of the putamen meet just lateral to the septum pellucidum. The nucleus accumbens, the ventral olfactory tubercle, and ventral caudate and putamen collectively form the ventral striatum. This nucleus is thought to play an important role in reward, pleasure, and addiction. It is part of the ventral continuation of the dorsal striatum, and shares general principles of connectivity with the striatum. The nucleus accumbens is also called ventral striatum. The principal neuronal cell type found in the nucleus accumbens is the medium spiny neuron. The neurotransmitter produced by these neurons is Gamma-Amino Butyric Acid, GABA, the main inhibitory neurotransmitter of the central nervous system. These neurons are also the main projection or output neurons of the nucleus accumbens. While 95% of the neurons in the nucleus accumbens are medium spiny GABAergic projection neurons, other neuronal types are also found such as large aspiny cholinergic interneurons. The output neurons of the nucleus accumbens send axon projections to the ventral analog of the globus pallidus, known as the ventral pallidum (VP). The VP, in turn, projects to the mediodorsal (MD) nucleus of the thalamus, which projects to the prefrontal cortex. Major inputs to the nucleus accumbens include the prefrontal cortex, amygdala, hippocampus, and dopaminergic neurons located in the ventral tegmental area (VTA), which connect via the mesolimbic pathway. Thus the nucleus accumbens is often described as one part of a cortico-striato-thalamo-cortical loop. Dopaminergic input from the VTA is thought to modulate the activity of neurons within the nucleus accumbens. These terminals are also the site of action of highly-addictive drugs such as cocaine and amphetamine, which cause a several-fold increase in dopamine levels in the nucleus accumbens. In addition to cocaine and amphetamine, almost every drug abused by humans has been shown to increase dopamine levels in the nucleus accumbens. Although the nucleus accumbens has traditionally been studied for its role in addiction, it plays an equal role in processing natural rewards such as food, sex, and video games.



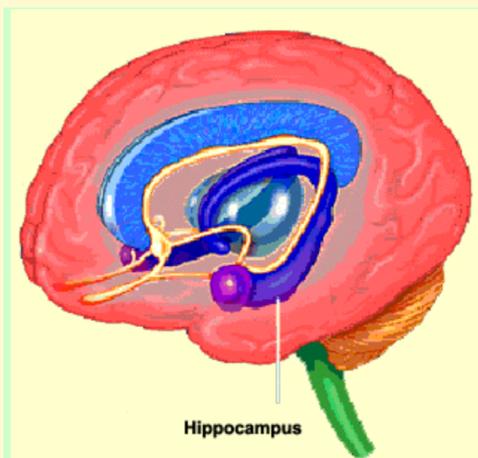
**Ventral Tegmental Area (VTA)** is part of the midbrain, lying close to the substantia nigra and the red nucleus. It is rich in dopamine and serotonin neurons, and is part of two major dopamine pathways: 1. the mesolimbic pathway, which connects the VTA to the nucleus accumbens; 2. the mesocortical pathway, which connects the VTA to cortical areas in the frontal lobes. The ventral tegmentum is considered to be part of the pleasure system, or reward circuit, one of the major sources of incentive and behavioural motivation. Activities that produce pleasure tend to activate the ventral tegmentum, and psychostimulant drugs (such as cocaine) directly target this area. Hence, it is widely implicated in neurobiological theories of addiction. It is also shown to process various types of emotion and security motivation, where it may also play a role in avoidance and fear-conditioning.



**Prefrontal Cortex (PFC)** is the anterior part of the frontal lobes of the brain, lying in front of the motor and premotor areas. Cytoarchitecturally, it is defined by the presence of an internal granular layer IV (in contrast to the agranular premotor cortex). Divided into the lateral, orbitofrontal and medial prefrontal areas, this brain region has been implicated in planning complex cognitive behaviors, personality expression and moderating correct social behavior. The basic activity of this brain region is considered to be orchestration of thoughts and actions in accordance with internal goals. The most typical neurologic term for functions carried out by the pre-frontal cortex area is Executive Function. Executive Function relates to abilities to differentiate between conflicting thoughts, determine good and bad, better and best, same and different, future consequences of current activities, working toward a defined goal, prediction of outcomes, expectation based on actions, and social "control" (the ability to suppress urges that, if not suppressed, could lead to socially unacceptable or illegal outcomes). Many authors have indicated an integral link between a person's personality and the functions of the prefrontal cortex.



**Locus coeruleus (LC)**, also spelled locus caeruleus or locus coeruleus (Latin for 'the blue spot'), is a nucleus in the brain stem responsible for physiological responses to stress and panic. The locus coeruleus (or "LC") resides on the dorsal wall of the upper pons, under the cerebellum in the caudal midbrain, surrounded by the fourth ventricle. This nucleus is one of the main sources of norepinephrine in the brain, and is composed of mostly medium-sized neurons. Melanin granules inside the LC contribute to its blue color; it is thereby also known as the nucleus pigmentosus pontis, meaning "heavily pigmented nucleus of the pons". The neuromelanin is formed by the polymerization of norepinephrine and is analogous to the black dopamine-based neuromelanin in the substantia nigra. The projections of this nucleus reach far and wide, innervating the spinal cord, the brain stem, cerebellum, hypothalamus, the thalamic relay nuclei, the amygdala, the basal telencephalon, and the cortex. The norepinephrine from the LC has an excitatory effect on most of the brain, mediating arousal and priming the brain's neurons to be activated by stimuli. It has been said that a single noradrenergic neuron can innervate, via its branches, the entire cerebral cortex.



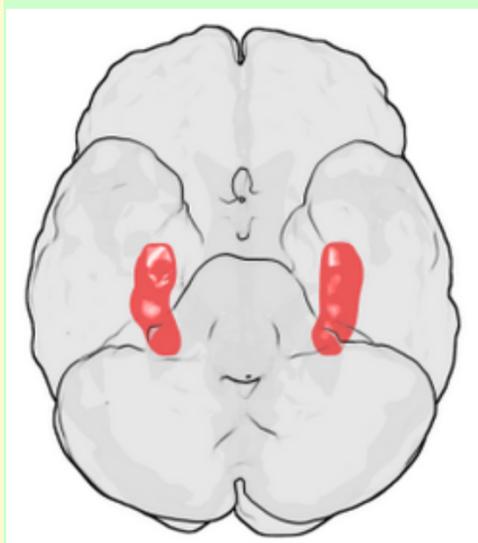
**Hippocampus** is a part of the brain located inside the temporal lobe (humans have two hippocampi, one in each side of the brain). It forms a part of the limbic system and plays a part in memory and navigation. The name derives from its curved shape in coronal sections of the brain, which to some resembles a seahorse (Greek: hippocampus). In Alzheimer's disease, the hippocampus becomes one of the first regions of the brain to suffer damage; memory problems and disorientation appear amongst the first symptoms. Damage to the hippocampus can also result from oxygen starvation (anoxia) and encephalitis. In the anatomy of animals, the hippocampus is among the phylogenetically oldest parts of the brain. The hippocampal emergence from the archipallium is most pronounced in primates and Cetacean sea mammals. Nonetheless, in primates the hippocampus occupies less of the telencephalon in proportion to cerebral cortex among the youngest species, especially humans. The significant development of hippocampal volume in primates correlates more with overall increase of brain mass than with neocortical development.

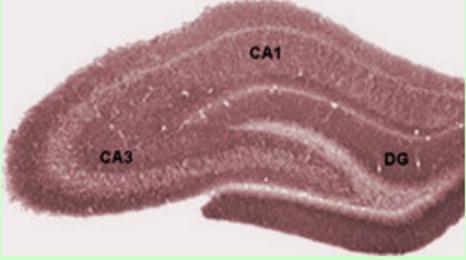
Although there is a lack of consensus relating to terms describing the hippocampus and the adjacent cortex, the term hippocampal formation generally applies to the dentate gyrus, fields CA1-CA3 (or CA4, frequently called the hilus and considered part of the dentate gyrus), and the subiculum (see also Cornu ammonis). The CA1 and CA3 fields make up the hippocampus proper.

Information flow through the hippocampus proceeds from dentate gyrus to CA3 to CA1 to the subiculum, with additional input information at each stage and outputs at each of the two final stages. CA2 represents only a very small portion of the hippocampus and its presence is often ignored in accounts of hippocampal function, though it is notable that this small region seems unusually resistant to conditions that usually cause large amounts of cellular damage, such as epilepsy.

The perforant path, which brings information primarily from entorhinal cortex (but also perirhinal cortex, among others), is generally considered the main source of input to the hippocampus. Layer II of entorhinal cortex (EC) brings input to the dentate gyrus and field CA3, while EC layer III brings input to field CA1 and the subiculum. The main output pathways of the hippocampus are the perforant path, the cingulum bundle, and the fimbria/fornix, which all arise from field CA1 and the subiculum.

Perforant path input from EC layer II enters the dentate gyrus and is relayed to region CA3 (and to mossy cells, located in the hilus of the dentate gyrus, which then send information to distant portions of the dentate gyrus where the cycle is repeated). Region CA3 combines this input with signals from EC layer II and sends





extensive connections within the region and also sends connections to region CA1 through a set of fibers called the Schaffer collaterals. Region CA1 receives input from region CA3 as well as EC layer III and then projects to the subiculum as well as sending information along the aforementioned output paths of the hippocampus. The subiculum is the final stage in the pathway, combining information from the CA1 projection and EC layer III to also send information along the output pathways of the hippocampus.

It is widely accepted that each of these regions has a unique functional role in the information processing of the hippocampus, but to date the specific contribution of each region is poorly understood.

#### Role in general memory

Drawing of the neural circuitry of the rodent hippocampus. S. Ramón y Cajal, 1911. Psychologists and neuroscientists dispute the precise role of the hippocampus, but, in general, agree that it has an essential role in the formation of new memories about experienced events (episodic or autobiographical memory). Some researchers prefer to consider the hippocampus as part of a larger medial temporal lobe memory system responsible for general declarative memory (memories that can be explicitly verbalized — these would include, for example, memory for facts in addition to episodic memory).

Some evidence supports the idea that, although these forms of memory often last a lifetime, the hippocampus ceases to play a crucial role in the retention of the memory after a period of consolidation. Damage to the hippocampus usually results in profound difficulties in forming new memories (anterograde amnesia), and normally also affects access to memories prior to the damage (retrograde amnesia). Although the retrograde effect normally extends some years prior to the brain damage, in some cases older memories remain - this sparing of older memories leads to the idea that consolidation over time involves the transfer of memories out of the hippocampus to other parts of the brain. However, experimentation has difficulties in testing the sparing of older memories; and, in some cases of retrograde amnesia, the sparing appears to affect memories formed decades before the damage to the hippocampus occurred, so its role in maintaining these older memories remains controversial.

Damage to the hippocampus does not affect some aspects of memory, such as the ability to learn new skills (playing a musical instrument, for example), suggesting that such abilities depend on a different type of memory (procedural memory) and different brain regions. And there is evidence (e.g., O'Kane et al 2004) to suggest that patient HM (who had his medial temporal lobes removed bilaterally as a treatment for epilepsy) can form new semantic memories.

#### Role in spatial memory and navigation

Some evidence implicates the hippocampus in storing and processing spatial information. Studies in rats have shown that neurons in the hippocampus have spatial firing fields. These cells are called place cells. Some cells fire when the animal finds itself in a particular location, regardless of direction of travel, while most are at least partially sensitive to head direction and direction of travel. In rats, some cells, termed splitter cells, may alter their firing depending on the animal's recent past (retrospective) or expected future (prospective). Different cells fire at different locations, so that, by looking at the firing of the cells alone, it becomes possible to tell where the animal is. Place cells have now been seen in humans involved in finding their way around in a virtual reality town. The findings resulted from research with individuals that had electrodes implanted in their brains as a diagnostic part of surgical treatment for serious epilepsy.

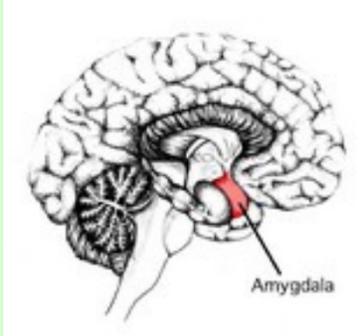
The discovery of place cells led to the idea that the hippocampus might act as a cognitive map — a neural representation of the layout of the environment. Recent evidence has cast doubt on this perspective, indicating that the hippocampus might be crucial for more fundamental processes within navigation[citation needed]. Regardless, studies with animals have shown that an intact hippocampus is required for simple spatial memory tasks (for instance, finding the way back to a hidden goal).

Without a fully-functional hippocampus, humans may not successfully remember the places they have been to and how to get where they are going. Researchers believe that the hippocampus plays a particularly important role in finding shortcuts and new routes between familiar places. Some people exhibit more skill at this sort of navigation than do others, and brain imaging shows that these individuals have more active hippocampi when navigating.

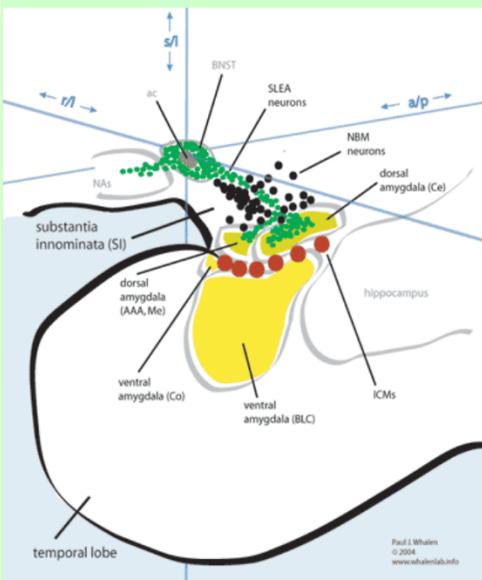
London's taxi drivers must learn a large number of places — and know the most direct routes between them (they have to pass a strict test, The Knowledge, before being licensed to drive the famous black cabs). A study at University College London (Maguire et al, 2000) showed that part of the hippocampus is larger in taxi drivers than in the general public, and that more-experienced drivers have bigger hippocampi. Whether having a bigger hippocampus helps an individual to become a cab driver or finding shortcuts for a living makes an individual's hippocampus grow is yet to be elucidated.

A study on rats at Indiana University suggested that the sexual dimorphism in the hippocampus morphology is tied to a sexual dimorphism in repeated maze performance. Males seem to be better at contextualizing their whereabouts because they have more hippocampus to work with.

**Amygdala** (Latin, corpus amygdaloideum) is an almond-shaped set of neurons located deep in the brain's medial temporal lobe. Shown to play a key role in the processing of emotions, the amygdala forms part of the



limbic system. In humans and other animals, this subcortical brain structure is linked to both fear responses and pleasure. Its size is positively correlated with aggressive behavior across species. In humans, it is the most sexually-dimorphic brain structure, and shrinks by more than 30% in males upon castration. Conditions such as anxiety, autism, depression, post-traumatic stress disorder, and phobias are suspected of being linked to abnormal functioning of the amygdala, owing to damage, developmental problems, or neurotransmitter imbalance. The amygdala is actually several separately-functioning nuclei that anatomists group together by the proximity of the nuclei to one another. Key among these nuclei are the basolateral complex, the centromedial nucleus, and the cortical nucleus.



The basolateral complex can be further subdivided into the lateral, the basal, and accessory basal nuclei. The lateral amygdala, which is afferent to both the rest of the basolateral complex as well as the centromedial nucleus, receives input from the sensory systems and is necessary for fear conditioning in rats. The centromedial nucleus is the main output for the basolateral complex, and is involved in emotional arousal in rats and cats. The amygdala sends outputs to the hypothalamus for activation of the sympathetic nervous system, the reticular nucleus for increased reflexes, the nuclei of the trigeminal nerve and facial nerve for facial expressions of fear, and the ventral tegmental area, locus ceruleus, and laterodorsal tegmental nucleus for activation of dopamine, norepinephrine and epinephrine. The cortical nucleus is involved in olfaction and pheromone-processing. It receives input from the olfactory bulb and olfactory cortex.

#### Emotional learning and memory

A key function of the amygdala in complex vertebrates, including humans, is the forming and storing of memories of emotional events. Damage to the amygdala impairs both the acquisition and expression of Pavlovian fear conditioning, a form of classical conditioning of emotional responses. Considerable research indicates that, during fear conditioning, sensory stimuli reach the basolateral complex, particularly the lateral nucleus of the amygdala, where they become associated. The association between stimuli and the aversive events they predict may be mediated by long-term potentiation, a form of long-lasting synaptic plasticity. Memories of emotional experiences stored in lateral nucleus synapses elicit fear behavior through connections with the central nucleus of the amygdala, a center involved in the genesis of many fear responses, including freezing (immobility), tachycardia (rapid heartbeat), increased respiration, and stress-hormone release.

The amygdala also plays a role in appetitive (positive) conditioning. It seems that distinct neurons respond to positive and negative stimuli, but there is no clustering of these distinct neurons into clear anatomical nuclei [1].

The suppression of learned fear responses is an important goal of therapeutic interventions for disorders of fear and anxiety, such as post-traumatic stress disorder and phobias, in humans. Evidence suggests that the amygdala is involved not only in fear conditioning, but also in the extinction of fear responses. Extinction, which occurs when fear signals are presented alone several times, yields a reduction in fear responses to those signals. Extinction training does not eliminate the fear memory, however; it is accompanied by new learning that inhibits the original fear. It is interesting to note that extinction learning (at least for fear responses) may also require synaptic plasticity in the amygdala. Systematic desensitization is a type of behavioral therapy for anxiety that relies on extinction learning.

#### Memory modulation and drug addiction

The amygdala also plays a key role in the modulation of memory consolidation. Following any learning event, the long-term memory for the event is not instantaneously formed. Rather, information regarding the event is slowly put into long-term storage over time, a process referred to as memory consolidation, until it reaches a relatively permanent state. During the consolidation period, the memory can be modulated. In particular, it appears that emotional arousal following the learning event influences the strength of the subsequent memory for that event. Greater emotional arousal following a learning event enhances a person's retention of that event. Experiments have shown that administration of stress hormones to individuals immediately after they learn something enhances their retention when they are tested two weeks later. The amygdala, especially the basolateral amygdala, plays a key role in mediating the effects of emotional arousal on the strength of the memory for the event, as shown by many laboratories including that of James McGaugh. These laboratories have trained animals on a variety of learning tasks and found that drugs injected into the amygdala after training affect the animals' subsequent retention of the task. These tasks include basic Pavlovian tasks such as inhibitory avoidance (where a rat learns to associate a mild footshock with a particular compartment of an apparatus) and more complex tasks such as spatial or cued water maze (where a rat learns to swim to a platform to escape the water). If a drug that activates the amygdala is injected into the amygdala, the animal has better memory for the training in the task. If a drug that inactivates the amygdala is injected into it, the animal has impaired memory for the task.

Despite the importance of the amygdala in modulating memory consolidation, however, learning can occur without it, though such learning appears to be impaired, as in fear conditioning impairments following amygdala damage.

Evidence from work with humans indicates that the amygdala plays a similar role. Amygdala activity at the time of encoding information correlates with retention for that information. However, this correlation depends on the relative "emotionalness" of the information. More emotionally-arousing information increases amygdala activity, and that activity correlates with retention.

Experiments with rats also suggest that the amygdala is involved in learning about various cues with the



consumption of drugs of abuse. It is well-known that one of the major problems in drug addiction is that drug-associated cues induce significant craving in individuals, even if the individuals have not taken the drugs in a long time. The basolateral amygdala appears to play a key role in the initial learning of the association between cues and the rewards that they predict. In addition, inactivation of the basolateral amygdala prevents the ability of cues to induce reinstatement in rats in a drug self-administration paradigm.

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